

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C. 20231  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 16 June 2000 (16.06.00)	
<b>International application No.</b> PCT/US99/25706	<b>Applicant's or agent's file reference</b> 00537/184WO1
<b>International filing date</b> (day/month/year) 02 November 1999 (02.11.99)	<b>Priority date</b> (day/month/year) 02 November 1998 (02.11.98)
<b>Applicant</b> IGNATIOUS, Francis, X.	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

27 April 2000 (27.04.00)

☐ in a notice effecting later election filed with the International Bureau on:
2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b>  Manu Berrod  Telephone No.: (41-22) 338.83.38
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From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

TSAO, Rocky Y. et al  
FISH & RICHARDSON P.C.  
225 Franklin Street  
Boston, Massachusetts 02110-2804  
ETATS-UNIS D'AMERIQUE

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FISH & RICHARDSON, P.C.  
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NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing  
(day/month/year)

27.02.2001

Applicant's or agent's file reference

IMPORTANT NOTIFICATION

International application No.  
PCT/US99/25706

International filing date (day/month/year)  
02/11/1999

Priority date (day/month/year)  
02/11/1998

Applicant

BIOMEASURE INCORPORATED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

## 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

\* No Docketing Required \*

Reviewed By Practice Systems

Initials: XX

Reviewed By Billing Secretary

Initials: \_\_\_\_\_

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer

Luck, E [Signature]

Tel. +49 89 2399-8238



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## PATENT COOPERATION TREATY

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference 00537/184WO1		<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/25706		International filing date (day/month/year) 02/11/1999		Priority date (day/month/year) 02/11/1998
International Patent Classification (IPC) or national classification and IPC A61K47/48				
Applicant BIOMEASURE INCORPORATED et al.				
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>				
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input checked="" type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>				
Date of submission of the demand  27/04/2000		Date of completion of this report  27.02.2001		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer  Staber, B  Telephone No. +49 89 2399 8587		



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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/25706

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

**Description, pages:**

1-27 as originally filed

**Claims, No.:**

1-30 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/25706

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 27-30.

because:

- ☒ the said international application, or the said claims Nos. 27-30 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
  - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
  - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
  - ☐ no international search report has been established for the said claims Nos. .
2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
  - ☐ the computer readable form has not been furnished or does not comply with the standard.

## IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/25706

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:  
**see separate sheet**
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
- ☒ all parts.
- ☐ the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	4-30
	No:	Claims	1-3
Inventive step (IS)	Yes:	Claims	10, 16-30
	No:	Claims	1-9, 11-15
Industrial applicability (IA)	Yes:	Claims	1-26, 27-30 (see Separate Sheet)
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

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### **Section III**

Claims 27 to 30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

### **Section IV: Non-unity**

The problem underlying the present invention is to provide a polymer which can be used as a matrix onto which a therapeutic agent, such as a polypeptide can be selectively anchored.

The solution therefore is the provision of a biodegradable a polymer bearing non-polymerizable lactone ring wherein the polymer is selected from polyester, polyorthoester, polyphosphoester, polycarbonates, polyanhydrides, and polyphosphazenes.

In the prior art document EP-A-0 440 108, polymers in general, and polyester in particular are described that bear a non-polymerizable lactone ring (see Section V). Hence, the "biodegradable polymer" can no longer serve as the technical feature linking the selected polymeric materials together, so that according to those materials, the invention contains six different inventions:

- (1) polyester bearing non-polymerizable lactone ring as set out in claims 1(part), 2 (part), 3, 9, 10, 16, 17, and 18-30 (part)
- (2) polyorthoester bearing non-polymerizable lactone ring as set out in claims 1(part), 2 (part), 4, 11, 12 ,18-30 (part)
- (3) polyphosphoester bearing non-polymerizable lactone ring as set out in claims 1(part), 2 (part), 5, 13, 14 ,18-30 (part)
- (4) polycarbonates bearing non-polymerizable lactone ring as set out in claims 1(part), 2 (part), 6, 18-30 (part)
- (5) polyanhydrides bearing non-polymerizable lactone ring as set out in claims 1(part), 2 (part), 7, 18-30 (part)
- (6) polyphosphazenes bearing non-polymerizable lactone ring as set out in claims 1(part), 2 (part), 8, 15, 18-30 (part).

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## **Section V**

### **1. Novelty**

The present invention pertains to biodegradable polymers comprising a non-polymerizable lactone ring, biodegradable compositions comprising the polymer and a therapeutic agent, and the use of the compositions for sustained release of therapeutic agents.

Prior art document D1 (EP-A-0 440 108) discloses a method for curing a resin starting from a straight-chain resin containing a lactone ring. On page 6, lines 33 to 56 of D1, it is said that one possible method to introduce the lactone structure into the resin substrate is "...that a polymerizable unsaturated monomer containing a lactone structure is singly polymerized or copolymerized with another polymerizable monomer". Examples of the polymerizable unsaturated monomers are acrylic compounds containing six or seven membered lactone rings. It is the acrylic moiety which under (co-)polymerization while the lactone structures are not involved in the polymerization reaction. Consequently, the lactone ring present in the monomeric compound can be considered as being non-polymerizable.

Hence, it is the uncured starting material which represents a polymer to which a non-polymerizable lactone ring is attached wherein the polymer is selected from an acrylic resin, a polyamide resin, a polyester resin, an epoxy resin and a fluorine resin (cf. D1, p.6, l. 8-11; example 4).

D1 therefore takes away novelty of claims 1, 2 and 3 of the invention in the sense of Art. 33(2) PCT.

### **2. Inventive Step**

The present invention as defined in claims 1 to 17 provides polymers comprising a lactone ring. Even if D1 is not directed to biodegradable polymers, the incorporation of a non-specified lactone structure into a biocompatible polymer is an obvious alternative to the lactone-modified polymers of D1 which therefore cannot be regarded to involve an inventive step.

Hence, in the light of D1, claims 1 to 9 and 11 to 15 do not fulfil the criteria of Article 33(3) PCT.

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The incorporation of specific lactone rings into a polyester resin as set out in claim 10 as well as the ring opening reaction as mentioned in claims 16 and 17 cannot be deduced from the teaching of D1 dealing with quite a different problem, namely with the curing of lactone-containing resins.

In addition, D1 is silent about a complex comprising a lactone-modified polymeric matrix in combination with a therapeutic agent and the use of such a complex. Hence, claims 18 to 30 appear to fulfil the criteria of Art. 33(3) PCT.

### **3. Industrial Applicability**

For the assessment of the present claims 27 to 30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The ECO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>00537/184W01</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 99/ 25706</b>	International filing date (day/month/year) <b>02/11/1999</b>	(Earliest) Priority Date (day/month/year) <b>02/11/1998</b>
Applicant <b>BIOMEASURE INCORPORATED et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

**4. With regard to the title,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

**5. With regard to the abstract,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. The figure of the drawings to be published with the abstract is Figure No.**

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/25706

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/48 C08G64/00 C08G67/04 C08G79/02 C08G63/08

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C08G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 440 108 A (KANSAI PAINT CO LTD) 7 August 1991 (1991-08-07) preparation example 4 claims 1-9	1-3



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

23 March 2000

Date of mailing of the international search report

31/03/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3018

Authorized officer

Decocker, L

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/US 99/25706

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0440108 A	07-08-1991	JP 2098415 C	02-10-1996
		JP 3220238 A	27-09-1991
		JP 8016160 B	21-02-1996
		CA 2034865 A	26-07-1991
		DE 69118726 D	23-05-1996
		DE 69118726 T	29-08-1996
		EP 0673961 A	27-09-1995
		US 5629381 A	13-05-1997
		US 5696212 A	09-12-1997

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : <b>A61K 47/48, C08G 64/00, 67/04, 79/02, 63/08</b>		(11) International Publication Number: <b>WO 00/25826</b>
<b>A1</b>		(43) International Publication Date: 11 May 2000 (11.05.00)
(21) International Application Number: PCT/US99/25706		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 2 November 1999 (02.11.99)		
(30) Priority Data: 09/184,413 2 November 1998 (02.11.98) US 60/106,708 2 November 1998 (02.11.98) US		
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US 60/106,708 (CON) Filed on 2 November 1998 (02.11.98) US 09/184,413 (CON) Filed on 2 November 1998 (02.11.98)		
(71) Applicant (for all designated States except US): BIOMEASURE INCORPORATED [US/US]; 27 Maple Street, Milford, MA 01757-3650 (US).		
(72) Inventor; and		<b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(75) Inventor/Applicant (for US only): IGNATIUS, Francis, X. [IN/US]; 15 Eagle Rock Drive, Milville, MA 01529 (US).		
(74) Agents: TSAO, Y., Rocky et al.; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2805 (US).		
(54) Title: LACTONE BEARING ABSORBABLE POLYMERS		
(57) Abstract <p>The present invention pertains to biodegradable polymers comprising a non-polymerizable lactone, biodegradable compositions comprising the polymer and a therapeutic agent, the use of the compositions for the sustained release of therapeutic agents, wherein the therapeutic agent is reversibly immobilized on the polymer matrix using ionic complexation between the latent carboxylic groups present on the lactone bearing polymer matrix and a cationic group on the therapeutic agent.</p>		

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AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

JC08 Rec'd PCT/PTO 02 MAY 2001

-1-

Lacton Bearing Absorbable PolymersBackground of the Invention

5 The present invention pertains to biodegradable polymers comprising a lactone, biodegradable compositions comprising the polymer and a therapeutic agent, the use of the compositions for the sustained release of therapeutic agents, wherein the therapeutic agent is reversibly immobilized on the polymer matrix using ionic complexation between the latent carboxylic groups present on the lactone bearing polymer matrix and the cationic group on the therapeutic agent.

10 In order to overcome the multiple dosing regime associated with therapy involving therapeutic agents, which includes peptides and proteins, having a short *in vivo* half life, numerous technologies are being evaluated for the sustained release of these therapeutic agents. One of these technologies is the encapsulation of drugs in biodegradable matrices such as polyesters, polycarbonates, polyanhydrides, polyorthoesters, polyphosphazenes, polyphosphoesters and the like (see U.S. Patent No. 4,675,189; U.S. Patent No. 4,767,628; U.S. Patent No. 5,271,945; WO 93/20126; GB Patent No. 2,145,422). The biodegradable microparticles containing the therapeutic agent(s) slowly release to maintain an effective plasma level for several days or even for months. The release of the therapeutic agent is dictated by a variety of factors arising from the polymer matrix as well as the physical characteristics of the therapeutic agent, making it possible to engineer the release profile by properly selecting the parameters governing them. The biodegradable polymer matrix degrades *in vivo* to non-toxic metabolites, at rates depending on the chemical nature of the polymer.

25 However, one of the many problems, encountered during the encapsulation of therapeutic agents in such biodegradable matrices is the inherent incompatibility between the polymer matrix and the therapeutic agent, such as a polypeptide. This incompatibility often leads to poor encapsulation efficiency as manifested during the emulsion solvent evaporation process, described by the oil-in-water process (P. B. O'Donnell and J. W. McGinity in

Advanced Drug Delivery Reviews, 28(1997), 25-42.). Another consequence of the incompatibility between the polymer matrix and a therapeutic agent, is the formation of phase separated domains inside the microparticle. The release of a therapeutic agent from such a phase separated, non-homogenous system becomes non-predictable. One of the ways to overcome such incompatibility is to anchor the therapeutic agent onto a polymer matrix using reversible bonds such as ionic bonds. These ionic complexes are formed between carboxylic functionalities of the polyester and cationic groups of the therapeutic agent as described in the U.S. Patent No. 5,672,659. The carboxylic acid functionalized polyesters were obtained by the ring opening polymerization of lactones using hydroxycarboxylic acid as an 'initiator', whereby the molecular weight of the resulting polyester is controlled by the molar ratio of the hydroxycarboxylic acid with respect to the monomers. The hydroxy group present in the hydroxycarboxylic acid is expected to participate in the ring opening polymerization, producing telechelic polymers having hydroxy and carboxylic groups at the chain extremities. However, the presence of carboxylic group in the initiator can interfere with the polymerization, as discussed by Zhang et al, in Journal Polymer Science, Polymer Chemistry Ed. 1994, 32,2965.

In this context the teachings of the present invention become relevant.

Five membered ring lactones and certain six membered lactones (see review by Johns, D.H. et al., in Ring Opening Polymerization, edited by K.J. Ivin and T. Saegusa, Elsevier Applied Science Publishers, NY) are thermodynamically stable and are considered non-polymerizable under the normal conditions of polymerization described by the present invention. An active hydrogen present on a five membered ring lactone, can be used to initiate the polymerization of other lactones, without affecting the five membered ring lactone. Therefore the five membered ring lactones can be incorporated intact, without unfavorably affecting the polymerization as would have been the case when hydroxy carboxylic acids are used as the initiator. These five membered ring lactones can be selectively used to anchor a therapeutic agent such as a polypeptide either by ionic complexation or by covalent conjugation.

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Hashimoto et al., describe the synthesis of polyurethanes containing glucarodilactones and mannarodilactones by the reaction between the dihydroxy groups present on the dilactone with diisocyanates (Journal of Polymer Science: Part A, Polymer Chemistry 1995, 33, 1495). However, such monomers have  
5 never been used in the synthesis of polyesters, polyorthoesters, polyphosphazenes, polycarbonates, polyanhydrides, polyphosphoesters, and the like.

#### Summary of the Invention

In one aspect, the present invention is directed to a polymer bearing non-  
10 polymerizable lactone ring wherein the polymer is selected from the group consisting of polyester, polyorthoester, polyphosphoester, polycarbonates, polyanhydrides and polyphosphazenes and copolymers and blends thereof. Depending on the lactone ring starting material that is used to make the polymer bearing non-polymerizable lactone ring, there may be one or multiple lactone  
15 rings in the polymer bearing non-polymerizable lactone ring. This is described in more detail below.

The polymer bearing non-polymerizable lactone ring described immediately above can have the non-polymerizable lactone within the polymer chain or the non-polymerizable lactone can be bonded to one or both ends of  
20 the polymer chain.

A preferred polymer bearing non-polymerizable lactone ring is where the polymer is a polyester. A preferred embodiment of the immediately foregoing polymer is where the polyester is selected from the group consisting of polymers, copolymers or blends of L-lactide, DL-lactide, D-lactide, lactic acid, ε-caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1,4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol. More preferred is where the polyester is selected from the group consisting of L-lactide, DL-lactide, glycolide, and polyethylene glycol and the non-polymerizable  
25 lactone ring is selected from the group consisting of hydroxybutyrolactone, erythrinolactone, isopropylidene ribonolactone, isocitric acid lactone, mannanolactone, sacharodilactone and glucarodilactone.  
30

Another preferred polymer bearing non-polymerizable lactone ring is where the polymer is a polyorthoester. A preferred embodiment of the immediately foregoing polymer is where the polyorthoester is obtained from a diketene acetal and a dihydroxy non-polymerizable lactone bearing prepolymer.

- 5 A preferred embodiment of the immediately foregoing polymer is where the dihydroxy non-polymerizable lactone bearing prepolymer comprises a polyester selected from the group consisting of polymers, copolymers or blends of l-lactide, dl-lactide, lactic acid,  $\epsilon$ -caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol.

- Another preferred polymer bearing non-polymerizable lactone ring is where the polymer is a polyphosphoester. A preferred embodiment of the immediately foregoing polymer is where the polyphosphoester is obtained from
- 15 (C<sub>1</sub>-C<sub>18</sub>)alkylphospho-dichloridates, cycloalkylphosphodichloridates or arylphosphodichloridates and a dihydroxy non-polymerizable lactone bearing prepolymer. A preferred embodiment of the immediately foregoing polymer is where the dihydroxy non-polymerizable lactone bearing prepolymer comprises a polyester selected from the group consisting of polymers, copolymers or blends
- 20 of l-lactide, dl-lactide, lactic acid,  $\epsilon$ -caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol.

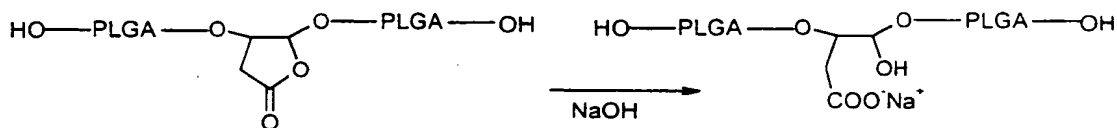
- Another preferred polymer bearing non-polymerizable lactone ring is
- 25 where the polymer is a polycarbonate.

Another preferred polymer bearing non-polymerizable lactone ring is where the polymer is a polyanhydride.

- Another preferred polymer bearing non-polymerizable lactone ring is where the polymer is a polyphosphazene. A preferred embodiment of the immediately foregoing polymer is where the polyphosphazene is obtained from
- 30 poly(dichloro)phosphazene and amino butyrolactone.

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In another aspect, the present invention is directed to a polymer bearing non-polymerizable lactone ring where the polymer is a polyester and wherein the non-polymerizable lactone has been ring opened to its corresponding hydroxycarboxylic acid alkali metal salt. For example, the following scheme shows a polymer bearing a non-polymerizable lactone bearing ring of the present invention before and after ring opening of the lactone ring, it is the ring opened product which is the object of this aspect of the present invention.



- 10 A preferred embodiment of the immediately foregoing polymer is where the polyester is selected from the group consisting of polymers, copolymers or blends of L-lactide, DL-lactide, D-lactide, lactic acid, ε-caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol, valerolactone, hydroxyvaleric acid, and butanediol. More preferred is when the polyester is selected from the group consisting of L-lactide, DL-lactide, glycolide, and polyethylene glycol and the hydroxycarboxylic acid corresponds to the ring opened product of the non-polymerizable lactone ring selected from the group consisting of hydroxybutyrolactone, erythrrolactone, isopropylidene ribonolactone, isocitric acid lactone, mannarolactone, sacharrodilactone and glucarodilactone. A most preferred embodiment of the foregoing polymer is where the hydroxycarboxylic acid alkali metal salt is within the polymer chain.
- 15
- 20

- In yet another aspect, the present invention provides a complex comprising a polymer bearing non-polymerizable lactone ring, ionically complexed with a therapeutic agent containing at least one cationic group, wherein the polymer is selected from the group consisting of polyester, polyorthoester, polyphosphoester, polycarbonates, polyanhydrides and polyphosphazenes, and copolymers and blends thereof. A preferred embodiment of the foregoing complex is where the polymer part of the polymer bearing non-polymerizable lactone ring is a polyester and wherein the non-
- 25
- 30

polymerizable lactone ring has been ring opened to its corresponding hydroxycarboxylic acid alkali metal salt, is ionically complexed with a therapeutic agent containing at least one cationic group. A preferred embodiment of the immediately foregoing polymer is where the polyester is selected from the group consisting of polymers, copolymers or blends of l-lactide, dl-lactide, d-lactide, lactic acid,  $\epsilon$ -caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1,4-dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol. More preferred is where the polyester is selected from the group consisting of l-lactide, dl-lactide, glycolide, and polyethylene glycol and the hydroxycarboxylic acid corresponds to the ring opened product of the non-polymerizable lactone ring selected from the group consisting of hydroxybutyrolactone, erythryrolactone, isopropylidene ribonolactone, isocitric acid lactone, mannarolactone, sacharrodilactone and glucarodilactone. A most preferred embodiment of the foregoing polymer is where the hydroxycarboxylic acid alkali metal salt is within the polymer chain. A further preferred embodiment of the foregoing complex is where the therapeutic agent is selected from the group consisting of LHRH, somatostatin, bombesin/GRP, calcitonin, bradykinins, galanin, MSH, GRF, amylin, tachykinin, secretin, PTH, CGRP, neuromedin, pTHRP, glucagon, neurotensin, ACTH, PYY, and TSH, or analogues or fragments thereof. An even more preferred embodiment of the foregoing complex is where the therapeutic agent is a somatostatin analogue selected from the group consisting of H- $\beta$ -D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>, where the two Cys are bonded by a disulfide bond, N-hydroxyethylpiperazinyl-acetyl-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub> where the two Cys are bonded by a disulfide bond or N-hydroxyethylpiperazinyl-ethylsulfonyl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub> where the two Cys are bonded by a disulfide bond or the therapeutic agent is an LHRH analogue of the formula p-Glu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH<sub>2</sub>.

In still another aspect, the present invention provides a sustained release composition comprising any one of the complexes described hereinabove.



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wherein the sustained release composition is in the form of microparticles, microspheres or rods.

In a further aspect, the present invention provides a pharmaceutical composition comprising any one of the complexes or sustained release  
5 compositions having an effective amount of the therapeutic agent, described hereinabove and a pharmaceutically-acceptable carrier.

In a yet further aspect, the present invention provides a method of treating or preventing a disease or a condition, which comprises administering any of the pharmaceutical compositions described hereinabove to a patient in  
10 need thereof, wherein said disease or condition is a disease or condition that can be treated by the therapeutic agent in the pharmaceutical composition.

In a still further aspect, the present invention provides a method of administering any of the complexes or pharmaceutical compositions described hereinabove to a recipient, wherein the pharmaceutical composition or complex  
15 is administered orally, through the nasal passage, through the pulmonary passage or parenterally.

The word "peptide" as used herein encompasses oligopeptides, polypeptides and proteins.

The term "therapeutic agent" encompasses any chemical entity that can  
20 be used to treat a disease or condition in a patient in need thereof, and, thus, includes peptides. Preferably the therapeutic agent contains a cationic moiety or can be modified by a cationic moiety, which cationic moiety can be used to form a complex with a polymer of the present invention.

The polymers of the present invention are typically biodegradable  
25 agents, that is it disassociates in the biological environment to inert by-products, which are used to complex a therapeutic agent to make a sustained release formulation of the therapeutic agent. This complex, which may be formed into various pharmaceutically-acceptable compositions such as microspheres, microparticles or rods, optionally comprising a pharmaceutically-acceptable  
30 carrier, is typically used to provide a sustained delivery of the therapeutic agent to a recipient thereof over a period of time ranging from one day to thirty days.

### Detailed Description of the Invention

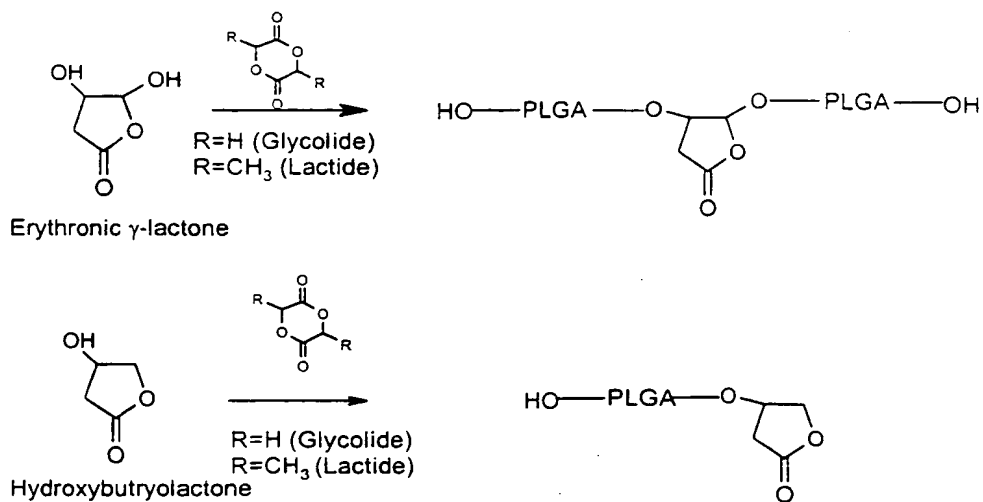
The lactone bearing biodegradable polymers of the invention are tailored to possess the desired chemical reactivity to provide controlled hydrolyzability and exhibit maximum binding capacity to a therapeutic agent having cationic groups, such as a peptide, by the selection of constituent monomers, co-  
5 monomers to form chains with predetermined compositions and molecular weights. A lactone bearing biodegradable polymer of this invention comprises a polymer selected from the group consisting of polyesters, polyorthoesters, polyphosphoesters, polycarbonates, polyanhydrides, polyphosphazenes  
10 polyoxalates, polyaminoacids, polyhydroxyalkanoates, polyethyleneglycol and copolymers and blends thereof, wherein the foregoing polymers can contain one or more of the following which may be present as polymers, prepolymers or copolymers: L-lactide, DL-lactide,  $\epsilon$ -caprolactone, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1,4-dioxepan-2-one, glycolide, ethylene glycol,  
15 propylene glycol, and/or butanediol.

The synthetic strategy employed to prepare compositions of the present invention comprise: synthesis of lactone bearing polymers; synthesis of ionic complexes between the lactone bearing polymer and the biologically active agent such as a peptide; and conversion of the ionic complexes to implants,  
20 rods, microspheres or microparticles, which are capable of slowly releasing the therapeutic agent *in vivo*.

Synthesis of lactone bearing polyesters: The lactone bearing polyesters can be synthesized by ring opening polymerization using a hydroxy or amino group present on a non-polymerizable lactone such as butyrolactone. Examples  
25 of non-polymerizable five membered lactones having at least one or more active hydrogen containing compound include, but are not limited to hydroxy butyrolactone, aminobutyrolactone, isopropylidene ribonolactone, mannarodilactone, sacharrodilactone, erythronolactone, and the like. The functional group in these non-polymerizable lactone can be used to regulate the  
30 ring opening polymerization of monomers or mixtures of monomers such as glycolide, lactide, caprolactone, valerolactone, cyclic carbonates, cyclic anhydrides, oxalates, and the like.

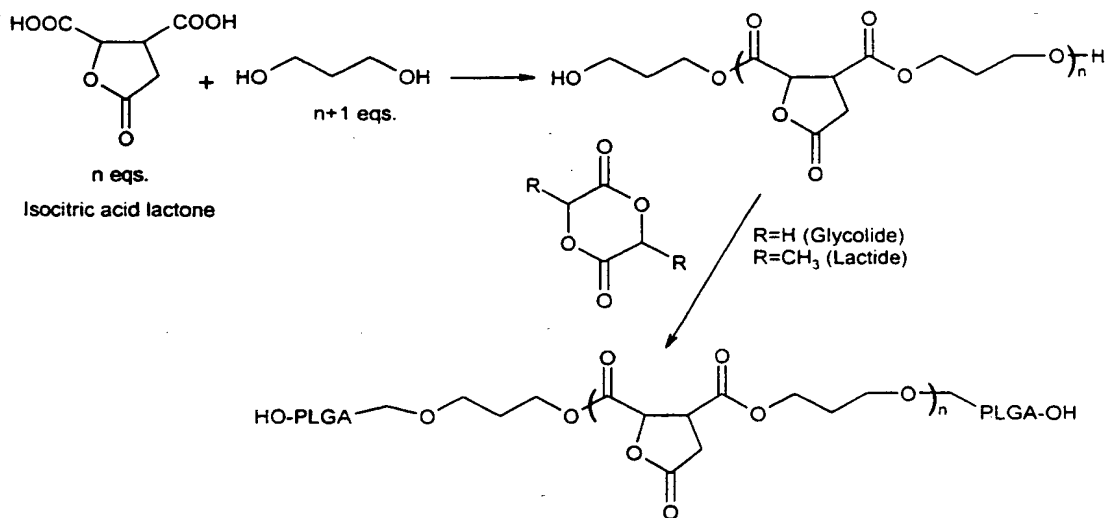
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Scheme 1



- Step growth polymerization between appropriate amounts of dicarboxylic acid present on a non-polymerizable five-membered lactone and diol, to obtain  $(\alpha, \omega)$  dihydroxy oligoester containing non-polymerizable lactone ring could also be used. The dihydroxy functionalities on the oligoester can be used to grow polymer chains to produce high molecular weight polyester, containing non-polymerizable lactone rings.

Scheme 2



Ring opening polymerization of a lactone or a lactone mixture in the presence of a predetermined concentration of hydroxy or amino groups present on a non-polymerizable lactone as a chain initiator and a catalytic amount of organometallic catalyst, e.g., a mixture of dl-lactide, glycolide and hydroxy butyrolactone, are weighed into a glass reactor in an oxygen free nitrogen filled dry box. Stannous octoate catalyst is added as a solution in toluene. Vacuum is applied to remove the toluene and the reactor is filled with dry argon and left at a positive pressure of argon. The reaction vessel is immersed in an oil bath at a suitable temperature between 120-200°C for polymerization for several hours. At the conclusion of the reaction, vacuum is applied to remove any residual monomer. The reaction vessel is cooled to room temperature and product is collected. The polymer obtained is further purified by dissolving in acetone, and precipitating in ten fold excess cold water. The precipitated polymer is collected by filtration. The product is dried under vacuum at 35°C.

The step growth polymerization which leads to ( $\alpha,\omega$ )-dihydroxy terminated oligoester containing non-polymerization lactone ring is performed by reacting appropriate amounts of a dicarboxylic acid functionalized lactone and diol, either at room temperature in the presence of coupling agents used in peptide chemistry such as N,N'-dicyclohexylcarbodiimide, N-hydroxybenzotriazole, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate, benzotriazole-1-yl-oxy-tris(dimethylamino)-phosphoniumhexafluorophosphate) or at high temperature wherein the water formed in the reaction is removed by azeotropization with a suitable organic solvent such as benzene, toluene or under a current of N<sub>2</sub> gas.

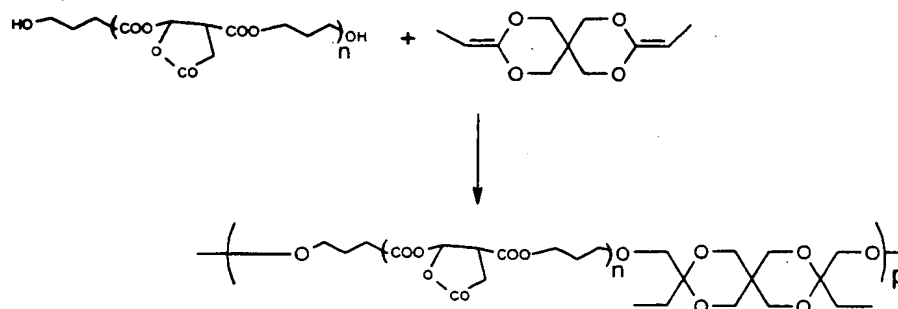
The simplest and the most versatile carboxylic functionalized five membered lactone is isocitric acid lactone, a Kreb's acid which would be metabolized *in vivo*. Examples of diols include simple diols as ethylene glycol, propylene glycol, butanediol, and ( $\alpha,\omega$ )-dihydroxy terminated oligomers or polymers such as polyethylene glycol, polypropylene glycol, polycaprolactone, polylactides, polyglycolides, polyanhydrides, polyorthoesters, or copolymers thereof. Or a diol may contain non-polymerizable five membered lactone, which may be polycondensed with a dicarboxylic acid. Examples of diols containing

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non-polymerizable lactones include but are not limited to mannarolactone, erythryrolactone, and the like. Dicarboxylic acids such as adipic, maleic, fumaric, glutaric, tartaric and the like may be used for polycondensation. The polycondensation may be optionally carried out in organic solvents such as dichloromethane, chloroform, tetrahydrofuran, dioxane, dimethylformamide, acetonitrile, dimethylsulfoxide, and the like in the presence of catalysts such as carbodiimide, benzotriazole, thionyl chloride, which are known in the art.

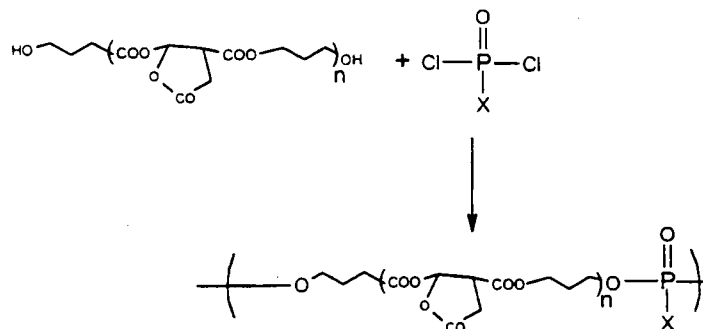
The product of the step growth polymerization may be obtained as a viscous liquid which gels on contact with water, depending on its hydrophilic-lipophilic balance (HLB value). It may be obtained as an amorphous powder by either driving the reaction to completion or by attaching polymer moieties by ring opening polymerization of lactides, glycolides, cyclic carbonates, cyclic anhydrides and the like, used as a mixture or individually to attain the desired properties. The molecular weight of the final polymer can be controlled by choosing the appropriate amount of prepolymer to the monomer. The polymer composition can also be tailored for a desired release profile of the therapeutic agent by appropriate choice of the monomers and molecular weight of the polymer.

Synthesis of a lactone bearing polymer of the instant invention comprising polyorthoesters can be realized according to the following scheme and substantially according to the procedures taught in Biomaterials, 19 (1998), 791-800, the contents of which are incorporated herein by reference.

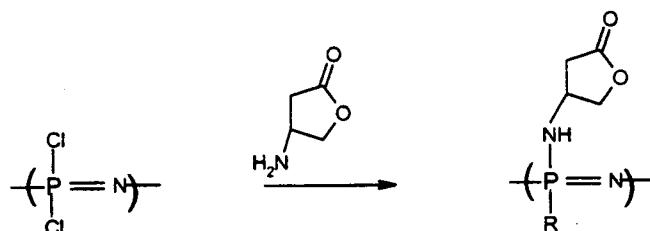


Synthesis of a lactone bearing polymer comprising polyphosphoesters can be accomplished by following the reaction scheme described below, and substantially according to the procedure described in U.S. Patent No. 5,256,765,

the contents of which are incorporated herein by reference, using a lactone bearing polymer in place of the polymer described therein.



A lactone bearing polymer comprising polyphosphazenes can be synthesized by the reaction between poly(dichlorophosphazene) and aminobutyrolactone, and substantially according to the procedure described in Chapter 9 of the Handbook of Biodegradable Polymers, edited by A.J. Domb, J. Kost and D.M. Wiseman, Hardwood Academic Publishers, the contents of which are incorporated herein by reference, using a lactone-bearing polymer in place of the polymer described therein.



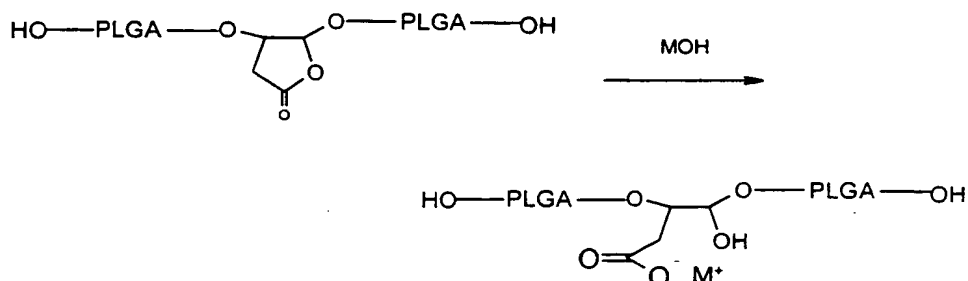
The polymer molecular weight determination is done by Gel Permeation Chromatography (GPC). The system consists of a Waters 6000A solvent delivery system (Waters Corporation, 26 Maple St., Milford, MA 01757), Dynamax Model AI-3 autoinjector (Ranin, Woburn, MA), Jordi Gel DVB Mixed bed (50x1 cm) column (Jordi Associates, Bellingham, MA) kept at a constant temperature using an Eppendorf CH-460 column heater (Madison, WI), Shimadzu RID-6A detector (Columbia, MD). The data is acquired using a Viscotek Data Manager DM-400 and Viscotek Trisec Software (Viscotek Corporation, Houston, TX). The molecular weights are calculated in comparison

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to a calibration curve constructed using Polystyrene molecular standards purchased from PolySciences, Inc., Warrington, PA.

Synthesis of polymer/peptide ionic complexes from lactone bearing polymer and cationic therapeutic agent:

- 5 All of the above lactone bearing polymers can be used to prepare ionic complexes with therapeutic agents, such as a peptide, having a cationic moiety. The lactone ring(s) present in these polymers can be opened by an alkali hydroxide to form alkali metal salt of the corresponding hydroxycarboxylic acid. In the case of  $\gamma$ -hydroxycarboxylic acid, it is known that the  $\gamma$ -hydroxycarboxylic acid always reverts back to the more thermodynamically favorable  $\gamma$ -lactone. Therefore, the presence of carboxylic groups in the latent lactone form does not enhance the acidic microenvironment within the polymer. A free acidic group can contribute towards the accelerated degradation of both the polyester and the polypeptide.



- 15 Examples of the physiologically active peptides that can form a complex with a lactone bearing polymer of the present invention include luteinizing hormone-releasing hormone (sometimes referred to as LHRH, gonadotropin-releasing hormone or Gn-RH), insulin, somatostatin, somatostatin derivative (Sandostatin®; see U.S. Patent Nos. 4,087,390, 4,093,574, 4,100,117 and 20 4,253,998; Lanreotide®; see U.S. Patent No. 4,853,371), growth hormones (GH), growth hormone-releasing hormones (GH-RH), prolactin, erythropoietin (EPO), adrenocorticotrophic hormone (ACTH), ACTH derivatives (e.g., ebitaride), melanocyte-stimulating hormone (MSH), thyrotropin-releasing hormone 25 (represented by the structural formula (Pyr)Glu-His-ProNH<sub>2</sub>, hereinafter also referred to as TRH) and salts and derivatives thereof (see Japanese Patent

Unexamined Publication Nos. 121273/1975 and 116465/1977), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), vasopressin, vasopressin derivative (desmopressin, see *Folia Endocrinologica Japonica*, Vol. 54, No. 5, pp. 676-691 (1978), oxytocin, 5 calcitonin, glucagon, gastrin, secretin, pancreozymin, cholecystokinin, angiotensin, human placental lactogen, human chorionic gonadotropin (HCG), enkephalin, enkephalin derivatives (see US Patent No. 4,277,394 and European Patent Publication No. 31567), endorphin, kyotorphin, interferons (e.g.,  $\alpha$ -,  $\beta$ - and  $\gamma$ -interferons), interleukins (e.g., interleukin 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 10 and 12) tuftsin, thymopoietin, thymosin, thymostimulin, thymic humoral factor (THF), blood thymic factor (FTS) and derivatives thereof (see U.S. Patent No. 4,229,438), tumor necrosis factor (TNF), colony-stimulating factors (e.g., CSF, GCSF, GMCSF, MCSF), motilin, dynorphin, bombesin, neurotensin, caerulein, 15 (NGF), cell growth factors (e.g., EGF, TGF- $\alpha$ , TGF- $\beta$ , PDGF, acidic FGF, basic FGF), nerve nutrition factors (e.g., NT-3, NT-4, CNTF, GDNF, BDNF), and endothelin-antagonistic peptides and their analogs (see European Patent Publication Nos. 436189, 457195 and 496452, and Japanese Patent Unexamined Publication Nos. 94692/1991 and 130299/1991), a protein derived 20 from  $\alpha$  1 domain of major histocompatibility class I antigen complex (Proceedings of the National Academy of Sciences of the United States of America, vol. 91, 9086-9090 (1994) and vol. 94, 11692-11697 (1997)) which has an activity of inhibiting an internalization of insulin receptor, insulin-like growth factor (IGF)-1 receptor, IGF-2 receptor, transferrin receptor, epidermal growth 25 factor receptor, low density lipoprotein (LDL) receptor, macrophage scavenger receptor, GLUT-4 transporter, growth hormone receptor and leptin receptor, and their analogs (derivatives), furthermore their fragments or derivatives thereof.

When the physiologically active peptides are salts, the salts include pharmacologically acceptable salts. Examples of the salts are salts formed with 30 inorganic acids (e.g., hydrochloric acid, sulfuric acid, nitric acid and boric acid) or salts formed with organic acids (e.g., carbonic acid, bicarbonic acid, succinic



acid, acetic acid, propionic acid and trifluoroacetic acid), when the physiologically active peptide has a basic group such as the amino group.

Examples of specific LHRH analogues that can form a complex with a lactone bearing polymer of the present invention include tryptorelin (p-Glu-His-  
5 Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH<sub>2</sub>), buserelin ([D-Ser(t-Bu)<sup>6</sup>, des-Gly-NH<sub>2</sub><sup>10</sup>]-LHRH(1-9)NHEt), deslorelin ([D-Trp<sup>6</sup>, des-Gly-NH<sub>2</sub><sup>10</sup>]-LHRH(1-9)NHEt, fertirelin ([des-Gly-NH<sub>2</sub><sup>10</sup>]-LHRH(1-9)NHEt), gosrelin ([D-Ser(t-Bu)<sup>6</sup>, Azgly<sup>10</sup>]-LHRH), histrelin ([D-His(Bzl)<sup>6</sup>, des-Gly-NH<sub>2</sub><sup>10</sup>]-LHRH(1-9)NHEt), leuprorelin ([D-Leu<sup>6</sup>, des-Gly-NH<sub>2</sub><sup>10</sup>]-LHRH(1-9)NHEt), lutrelin ([D-Trp<sup>6</sup>, MeLeu<sup>7</sup>, des-Gly-NH<sub>2</sub><sup>10</sup>]-  
10 LHRH(1-9)NHEt), nafarelin ([D-Nal<sup>6</sup>]-LHRH and pharmaceutically acceptable salts thereof.

Preferred somatostatin analogs that can form a complex with a lactone bearing polymer of the present invention include those covered by formulae or those specifically recited in the publications set forth below, all of which are  
15 incorporated herein by reference:

Van Binst, G. et al. Peptide Research 5:8 (1992);  
Horvath, A. et al. Abstract, "Conformations of Somatostatin Analogs Having Antitumor Activity", 22nd European peptide Symposium, September 13-19, 1992, Interlaken, Switzerland;  
20 PCT Application WO 91/09056 (1991);  
EP Application 0 363 589 A2 (1990);  
U.S. Patent No. 4,904,642 (1990);  
U.S. Patent No. 4,871,717 (1989);  
U.S. Patent No. 4,853,371 (1989);  
25 U.S. Patent No. 4,725,577 (1988);  
U.S. Patent No. 4,684,620 (1987)  
U.S. Patent No. 4,650,787 (1987);  
U.S. Patent No. 4,603,120 (1986);  
U.S. Patent No. 4,585,755 (1986);  
30 EP Application 0 203 031 A2 (1986);  
U.S. Patent No. 4,522,813 (1985);  
U.S. Patent No. 4,486,415 (1984);

- U.S. Patent No. 4,485,101 (1984);
- U.S. Patent No. 4,435,385 (1984);
- U.S. Patent No. 4,395,403 (1983);
- U.S. Patent No. 4,369,179 (1983);
- 5 U.S. Patent No. 4,360,516 (1982);
- U.S. Patent No. 4,358,439 (1982);
- U.S. Patent No. 4,328,214 (1982);
- U.S. Patent No. 4,316,890 (1982);
- U.S. Patent No. 4,310,518 (1982);
- 10 U.S. Patent No. 4,291,022 (1981);
- U.S. Patent No. 4,238,481 (1980);
- U.S. Patent No. 4,235,886 (1980);
- U.S. Patent No. 4,224,190 (1980);
- U.S. Patent No. 4,211,693 (1980);
- 15 U.S. Patent No. 4,190,648 (1980);
- U.S. Patent No. 4,146,612 (1979);
- U.S. Patent No. 4,133,782 (1979);
- U.S. Patent No. 5,506,339 (1996);
- U.S. Patent No. 4,261,885 (1981);
- 20 U.S. Patent No. 4,728,638 (1988);
- U.S. Patent No. 4,282,143 (1981);
- U.S. Patent No. 4,215,039 (1980);
- U.S. Patent No. 4,209,426 (1980);
- U.S. Patent No. 4,190,575 (1980);
- 25 EP Patent No. 0 389 180 (1990);
- EP Application No. 0 505 680 (1982);
- EP Application No. 0 083 305 (1982);
- EP Application No. 0 030 920 (1980);
- PCT Application No. WO 88/05052 (1988);
- 30 PCT Application No. WO 90/12811 (1990);
- PCT Application No. WO 97/01579 (1997);
- PCT Application No. WO 91/18016 (1991);

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U.K. Application No. GB 2,095,261 (1981); and  
French Application No. FR 2,522,655 (1983).

Examples of somatostatin analogs that can form a complex with a lactone bearing polymer of the present invention include, but are not limited to, the following somatostatin analogs which are disclosed in the above-cited references:

- H-D- $\beta$ -Nal-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;
- H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys- $\beta$ -Nal-NH<sub>2</sub>;
- H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys- $\beta$ -Nal-NH<sub>2</sub>;
- 10 H-D- $\beta$ -Nal-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;
- H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH<sub>2</sub>;
- H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-NH<sub>2</sub>;
- H-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-OH;
- H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Pen-Thr-OH;
- 15 H-Gly-Pen-Phe-D-Trp-Lys-Thr-Cys-Thr-OH;
- H-Phe-Pen-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH;
- H-Phe-Pen-Phe-D-Trp-Lys-Thr-Pen-Thr-OH;
- H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol;
- H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;
- 20 H-D-Trp-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;
- H-D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;
- H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;
- H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH<sub>2</sub>;
- H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;
- 25 Ac-D-Phe-Lys\*-Tyr-D-Trp-Lys-Val-Asp\*-Thr-NH<sub>2</sub> (an amide bridge formed between Lys\* and Asp\*);
- Ac-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;
- Ac-D-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;
- Ac-D-hArg(Bu)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;
- 30 Ac-D-hArg(Et)<sub>2</sub>-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;
- Ac-L-hArg(Et)<sub>2</sub>-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;
- Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;

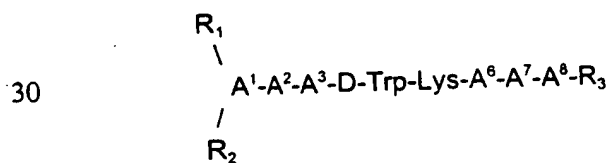
- Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
 Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH<sub>2</sub>;  
 Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHEt;  
 Ac-L-hArg(CH<sub>2</sub>-CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
 5 Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-NH<sub>2</sub>;  
 Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-NHEt;  
 Ac-hArg(CH<sub>3</sub>, hexyl)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
 H-hArg(hexyl)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
 Ac-D-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHEt;  
 10 Ac-D-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH<sub>2</sub>;  
 Propionyl-D-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys(iPr)-Thr-Cys-Thr-NH<sub>2</sub>;  
 Ac-D-β-Nal-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Gly-hArg(Et)<sub>2</sub>-NH<sub>2</sub>;  
 Ac-D-Lys(iPr)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
 Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-  
 15 NH<sub>2</sub>;  
 Ac-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-D-hArg(CH<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-  
 NH<sub>2</sub>;  
 Ac-D-hArg(Et)<sub>2</sub>-D-hArg(Et)<sub>2</sub>-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>;  
 Ac-Cys-Lys-Asn-4-Cl-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Ser-D-Cys-NH<sub>2</sub>;  
 20 H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;  
 H-Bmp-Tyr-D-Trp-Lys-Val-Cys-Phe-NH<sub>2</sub>;  
 H-Bmp-Tyr-D-Trp-Lys-Val-Cys-p-Cl-Phe-NH<sub>2</sub>;  
 H-Bmp-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH<sub>2</sub>;  
 H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;  
 25 H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub>;  
 H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH<sub>2</sub>;  
 H-pentafluoro-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;  
 Ac-D-β-Nal-Cys-pentafluoro-Phe-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;  
 H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH<sub>2</sub>;  
 30 H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH<sub>2</sub>;  
 H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub>;  
 H-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub>;

- Ac-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub>;  
H-D-Phe-Cys-β-Nal-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>;  
H-D-Phe-Cys-Tyr-D-Trp-Lys-Cys-Thr-NH<sub>2</sub>;  
cyclo(Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe);  
5 cyclo(Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe);  
cyclo(Pro-Phe-D-Trp-Lys-Thr-N-Me-Phe);  
cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Thr-Phe);  
cyclo(Pro-Tyr-D-Trp-Lys-Thr-Phe);  
cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe);  
10 cyclo(Pro-Phe-L-Trp-Lys-Thr-Phe);  
cyclo(Pro-Phe-D-Trp(F)-Lys-Thr-Phe);  
cyclo(Pro-Phe-Trp(F)-Lys-Thr-Phe);  
cyclo(Pro-Phe-D-Trp-Lys-Ser-Phe);  
cyclo(Pro-Phe-D-Trp-Lys-Thr-p-Cl-Phe);  
15 cyclo(D-Ala-N-Me-D-Phe-D-Thr-D-Lys-Trp-D-Phe);  
cyclo(D-Ala-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Phe);  
cyclo(D-Ala-N-Me-D-Phe-D-Thr-Lys-D-Trp-D-Phe);  
cyclo(D-Abu-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Tyr);  
cyclo(Pro-Tyr-D-Trp-t-4-AchxAla-Thr-Phe);  
20 cyclo(Pro-Phe-D-Trp-t-4-AchxAla-Thr-Phe);  
cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe);  
cyclo(N-Me-Ala-Tyr-D-Trp-t-4-AchxAla-Thr-Phe);  
cyclo(Pro-Tyr-D-Trp-4-Amphe-Thr-Phe);  
cyclo(Pro-Phe-D-Trp-4-Amphe-Thr-Phe);  
25 cyclo(N-Me-Ala-Tyr-D-Trp-4-Amphe-Thr-Phe);  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba-Gaba);  
cyclo(Asn-Phe-D-Trp-Lys-Thr-Phe);  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-NH(CH<sub>2</sub>)<sub>4</sub>CO);  
30 cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-β-Ala);  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-D-Glu)-OH;  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe);

- cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Gly);  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gly);  
cyclo(Asn-Phe-Phe-D-Trp(F)-Lys-Thr-Phe-Gaba);  
5 cyclo(Asn-Phe-Phe-D-Trp(NO<sub>2</sub>)-Lys-Thr-Phe-Gaba);  
cyclo(Asn-Phe-Phe-Trp(Br)-Lys-Thr-Phe-Gaba);  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Phe(I)-Gaba);  
cyclo(Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr(But)-Gaba);  
cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-Cys)-OH;  
10 cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Pro-Cys)-OH;  
cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Tpo-Cys)-OH;  
cyclo(Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-MeLeu-Cys)-OH;  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-Phe-Gaba);  
cyclo(Phe-Phe-D-Trp-Lys-Thr-Phe-D-Phe-Gaba);  
15 cyclo(Phe-Phe-D-Trp(5F)-Lys-Thr-Phe-Phe-Gaba);  
cyclo(Asn-Phe-Phe-D-Trp-Lys(Ac)-Thr-Phe-NH-(CH<sub>2</sub>)<sub>3</sub>-CO);  
cyclo(Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);  
cyclo(Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);  
cyclo(Orn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);  
20 H-Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys-NH<sub>2</sub>;  
H-Cys-Phe-Phe-D-Trp-Lys-Ser-Phe-Cys-NH<sub>2</sub>;  
H-Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys-NH<sub>2</sub>; and  
H-Cys-Phe-Tyr(I)-D-Trp-Lys-Thr-Phe-Cys-NH<sub>2</sub>.

25 A disulfide bridge is formed between the two free thiols (e.g., Cys, Pen, or Bmp residues) when they are present in a peptide; however, the disulfide bond is not shown.

Also included are somatostatin agonists of the following formula:



wherein

A<sup>1</sup> is a D- or L- isomer of Ala, Leu, Ile, Val, Nle, Thr, Ser, β-Nal, β-Pal,

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Trp, Phe, 2,4-dichloro-Phe, pentafluoro-Phe, p-X-Phe, or o-X-Phe, wherein X is CH<sub>3</sub>, Cl, Br, F, OH, OCH<sub>3</sub> or NO<sub>2</sub>;

A<sup>2</sup> is Ala, Leu, Ile, Val, Nle, Phe, β-Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH<sub>3</sub>, Cl, Br, F, OH, OCH<sub>3</sub> or NO<sub>2</sub>;

A<sup>3</sup> is pyridyl-Ala, Trp, Phe, β-Nal, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH<sub>3</sub>, Cl, Br, F, OH, OCH<sub>3</sub> or NO<sub>2</sub>;

A<sup>6</sup> is Val, Ala, Leu, Ile, Nle, Thr, Abu, or Ser;

A<sup>7</sup> is Ala, Leu, Ile, Val, Nle, Phe, β-Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH<sub>3</sub>, Cl, Br, F, OH, OCH<sub>3</sub> or NO<sub>2</sub>;

A<sup>8</sup> is a D- or L-isomer of Ala, Leu, Ile, Val, Nle, Thr, Ser, Phe, β-Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, p-X-Phe, or o-X-Phe, wherein X is CH<sub>3</sub>, Cl, Br, F, OH, OCH<sub>3</sub> or NO<sub>2</sub>;

each R<sub>1</sub> and R<sub>2</sub>, independently, is H, lower acyl or lower alkyl; and R<sub>3</sub> is OH or NH<sub>2</sub>; provided that at least one of A<sup>1</sup> and A<sup>8</sup> and one of A<sup>2</sup> and A<sup>7</sup> must be an aromatic amino acid; and further provided that A<sup>1</sup>, A<sup>2</sup>, A<sup>7</sup> and A<sup>8</sup> cannot all be aromatic amino acids.

Examples of linear agonists that can form a complex with a lactone bearing polymer of the present invention include:

H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH<sub>2</sub>;

H-D-Phe-p-NO<sub>2</sub>-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>;

H-D-Nal-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>;

H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH<sub>2</sub>;

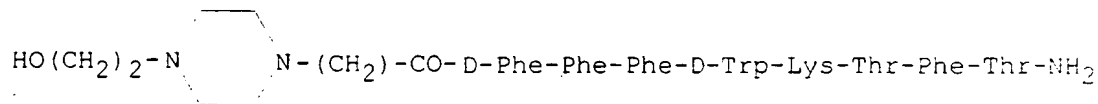
H-D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>;

H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>; and

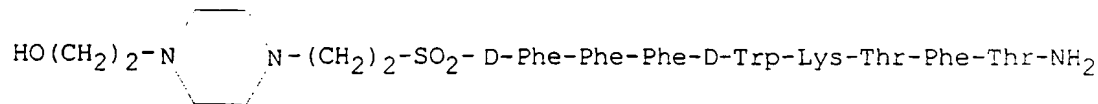
H-D-Phe-Ala-Tyr-D-Trp-Lys-Val-Ala-β-D-Nal-NH<sub>2</sub>.

If desired, one or more chemical moieties, e.g., a sugar derivative, mono or poly-hydroxy C<sub>2-12</sub> alkyl, mono or poly-hydroxy C<sub>2-12</sub> acyl groups, or a piperazine derivative, can be attached to the somatostatin agonist, e.g., to the N-terminus amino acid. See PCT Application WO 88/02756, European Application 0 329 295, and PCT Application No. WO 94/04752. An example of

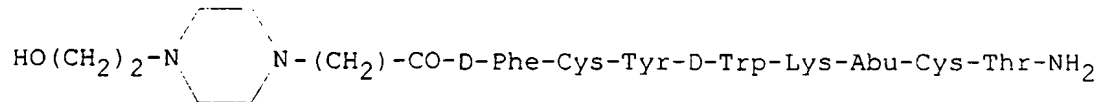
somatostatin agonists which contain N-terminal chemical substitutions are:



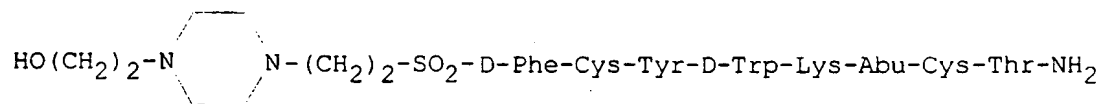
;



5 ;



; and



10        The formation of the ionic complexes is achieved by direct molecular interaction of the components (lactone bearing polymer and therapeutic agent, such as a peptide) in an appropriate solvent with a pretreatment of the lactone bearing polymer with an inorganic base which results in the ring-opened hydroxycarboxylic acid corresponding to the lactone bearing polymer. The  
15        lactone bearing polymer is dissolved in a suitable aprotic solvent in a concentration range of 2-25 % (w/v). These organic solvents are either partially or completely miscible with water. Such solvents include acetone, tetrahydrofuran, acetonitrile, ethylene glycol, dimethyl ether, methyl formate, dioxane and the like. To this polymer solution, an aqueous solution of a base  
20        such as sodium, potassium or ammonium, calcium, hydroxide or carbonate or bicarbonate, is added to open the intact five membered cyclic lactone, to yield the corresponding metallic salts of hydroxycarboxylic acid. In general, the amount of the inorganic base used corresponds to the amount of counter-anion of the basic peptide.

25        The mixture of the metallic salts of hydroxycarboxylic acid polymer and the inorganic base are stirred and a solution of the therapeutic agent, such as a peptide, in a minimum amount of water either alone or in combination with the



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same organic solvent used for dissolving the peptide, is added. The amount of organic solvent to aqueous in the mixture is adjusted to get a clear solution which is left stirring for 1-2 hours. This solution is precipitated in ice cold water. The precipitate formed is collected by vacuum filtration and dried under vacuum.

- 5 The peptide content in the formulation is determined by nitrogen analysis performed by QTI, Whitehouse, NJ.

Conversion of ionic complexes to implants, rods, microspheres or microparticles:

- 10 The polymer-peptide ionic complexes of this invention can be converted to injectable dosage forms such as implants, rods, microspheres or microparticles by any of the relevant methods described in PCT International Publication Number WO 97/39738, the contents of which are incorporated herein by reference.

- 15 The pharmaceutical compositions of this invention can be administered to a patient via administration routes well known to those of ordinary skill in the art, such as parenteral administration, oral administration or topical administration. Preferably, it is administered as a powder or a suspension via intranasal route or as an inhalant through the pulmonary system. When it is administered parenterally it is preferable that it is administered as a dispersion in
- 20 an isotonic aqueous medium or in a non-aqueous, absorbable gel-forming liquid polyester as described in U.S. Patent No. 5,612,052, the contents of which are incorporated herein by reference. The formulations comprising microparticles of the present invention can also include a variety of optional components. Such components include, but are not limited to, surfactants, viscosity controlling
- 25 agents, medicinal agents, cell growth modulators, dyes, complexing agents, antioxidants, other polymers such as carboxymethyl cellulose, gums such as guar gum, waxes/oils such as castor oil, glycerol, dibutyl phthalate and di(2-ethylhexyl)phthalate as well as many others. If used, such optional components comprise from about 0.1% to about 20%, preferably from about 0.5% to about
- 30 5% of the total formulation.

Compositions or formulations of this invention can be used to treat a disease or condition in a patient in need thereof according to the use that is

known for the therapeutic agent, such as a peptide or peptides, which is in the composition, which are known to one of ordinary skill in the art. For example, microparticles of the present invention comprising a somatostatin analogue will be useful in treating a disease or condition that can be treated with somatostatin or an analogue thereof.

The effective dosages of a composition or formulation of the present invention to be administered to a patient can be determined by the attending physician or veterinarian and will be dependent upon the proper dosages contemplated for the therapeutic agent and the quantity of the therapeutic agent in the composition. Such dosages will either be known or can be determined by one of ordinary skill in the art without undue experimentation.

The following examples illustrate the present invention and are not to be construed to limit the scope of the present invention.

#### Example 1

Ring Opening Polymerization: Synthesis of 65/35 p(dl-lactide-co-glycolide) initiated by erythrrolactone:

DL-Lactide (43.8g, 0.3041M), glycolide (17.6g, 1517M), erythrrolactone (1g, 0.0084M) and 0.2ml stannous octoate catalyst were added to the reaction vessel provided with a mechanical stirrer. The reaction vessel was evacuated and purged with dry argon at least three times and then left at a positive pressure of argon. The reaction vessel was immersed in an oil bath kept at about 160°C. The reaction was allowed to proceed for about 6 hours. After completion of the reaction, the temperature was lowered to about 100°C and the vessel was evacuated to remove any residual monomer. The reaction vessel was cooled to room temperature, quenched in liquid N<sub>2</sub> and the polymer was collected. The polymer was further purified by preparing a 10% solution and precipitating in cold water. The precipitate was collected and dried under vacuum. Polymer molecular weight determined by GPC analysis is Mn= 7250, Mw=12700

#### Example 2

Ring opening polymerization: synthesis of p(dl-lactide) initiated by isopropylidene ribonolactone:

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DL-Lactide (60g, 0.4166M) and isopropylidene ribonolactone (2.35g, 0.0125M) were polymerized according to the procedure described in Example 1. The molecular weights of the polymer obtained determined by GPC analysis is Mn=5050, Mw=7980.

5

Example 3

Step growth polymerization and subsequent ring opening polymerization: Preparation of polyethylene glycol-co-poly(lactide-co-glycolide) copolymers containing butyrolactone

Isocitric acid (Aldrich Chemicals, St. Louis, MO) (2.5g, .0143M) and polyethylene glycol-400 were mixed in a three necked round bottom flask, along with 50ml of toluene. The toluene was refluxed at about 130°C to azeotropically remove the water formed during the reaction by using a Dean-Stark apparatus. After about 48h, the toluene was completely removed by distillation, and DL-lactide (30g, 0.2082M), and glycolide (16.1g, 0.1388M) were added along with 0.2ml stannous octoate catalyst in toluene. The temperature of the reaction vessel was raised to about 160°C and the polymerization was carried out for about 6h. At the end of the polymerization, the reaction vessel was evacuated to remove any residual monomer.

15

Example 4

Step growth polymerization and subsequent ring opening polymerization:

Isocitric acid lactone (2.5g, 0.0143M) and propanediol (1.202g, 0.0157M) were mixed and reacted at about 90°C, under refluxing benzene. The water formed was removed by azeotropization with a Dean-Stark trap. The reaction was allowed to proceed overnight, after which benzene was removed by distillation to yield a viscous liquid which solidifies on cooling.

25

The reaction vessel was transferred to a dry-box and 25.2g of dl-lactide and 7.25g of glycolide were added along with 0.2ml stannous octoate solution in toluene. The reaction vessel was purged with dry argon and the polymerization was performed at about 160°C for about 8h. The polymer was quenched in liquid N<sub>2</sub>, collected and dissolved in acetone and precipitated in cold water. The filtered polymer was dried under vacuum at about 40°C. Mn= 3790, Mw= 7040, as determined by GPC.

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#### Example 5

Synthesis of ionic complexes of polymer synthesized in Example 4 and Lanreotide® using 1N NaOH as the base:

One gram of polymer dissolved in acetone was treated with 0.45ml 1N NaOH. The solution was stirred for about 20 min, and 0.29g of Lanreotide® (Kinerton, Ltd., Dublin, Ireland; Lanreotide has the formula: H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub> where the two Cys are bonded by a disulfide bond), dissolved in 2ml of 1:1 acetone/water was added to the polymer solution. The polymer solution was left stirring for about 2h, and then it was precipitated in cold water. The product was filtered and vacuum dried. The peptide content in the formulation determined by nitrogen analysis was 17.6%.

#### Example 6

Synthesis of ionic complexes of the polymer synthesized in Example 4 and Lanreotide® using NaHCO<sub>3</sub> as the base:

One gram of the polymer made in Example 4 dissolved in acetone was treated with 0.45ml of 1N NaHCO<sub>3</sub>. The solution was stirred for about 20min, and 0.29g of Lanreotide® dissolved in 2ml of 1:1 acetone/water was added to the polymer solution. The polymer solution was left stirring for about 2h, and it was precipitated in cold water. The product was filtered and vacuum dried. The peptide content in the formulation determined by nitrogen analysis was 17.6%.

#### Example 7

*In vivo* testing of the samples prepared in Examples 5 and 6:

Samples from Examples 5 & 6 were each separately ground and sieved with a mortar and pestle, and sieved using a 125 micron sieve. Rats were administered 6.75mg of peptide equivalent per rat, using an injection medium consisting of 2% carboxymethylcellulose, 1% Tween 20® (Aldrich Chemicals, St. Louis, MO) and saline. Blood samples were collected at various time intervals and the plasma Lanreotide® levels were determined by radioimmuno assay. The plasma Lanreotide® levels (ng/ml) for the two samples tested are shown in Table I below.

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TABLE I

Sample/Time	6h	Day 2	Day 8	Day 15	Day 22
Example 5	21.7± 4.5	30.3±2.7	30.2±7.5	0.8±0.3	0.05±0.02
Example 6	24.4±5.2	31.4±5.8	20.8±7.2	1.4±1.2	0.141±0.09

### CLAIMS

What is claimed is:

1. A polymer bearing non-polymerizable lactone ring wherein the polymer is selected from the group consisting of polyester, polyorthoester, polyphosphoester, polycarbonates, polyanhydrides and polyphosphazenes and copolymers and blends thereof.
2. A polymer bearing non-polymerizable lactone ring according to claim 1 wherein the non-polymerizable lactone ring is within the polymer chain or the non-polymerizable lactone ring is bonded to one or both ends of the polymer chain.
3. A polymer bearing non-polymerizable lactone ring according to claim 2, wherein the polymer is a polyester.
4. A polymer bearing non-polymerizable lactone ring according to claim 2, wherein the polymer is a polyorthoester.
5. A polymer bearing non-polymerizable lactone ring according to claim 2, wherein the polymer is a polyphosphoester.
6. A polymer bearing non-polymerizable lactone ring according to claim 2, wherein the polymer is a polycarbonate.
7. A polymer bearing non-polymerizable lactone ring according to claim 2, wherein the polymer is a polyanhydride.
8. A polymer bearing non-polymerizable lactone ring according to claim 2, wherein the polymer is a polyphosphazene.
9. A polymer bearing non-polymerizable lactone ring according to claim 3, wherein the polyester is selected from the group consisting of polymers, copolymers or blends of l-lactide, dl-lactide, d-lactide, lactic acid,  $\epsilon$ -caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol.
10. A polymer bearing non-polymerizable lactone ring according to claim 9, wherein the polyester is selected from the group consisting of l-lactide, dl-lactide, glycolide, and polyethylene glycol and the non-polymerizable lactone ring is selected from the group consisting of hydroxybutyrolactone,

erythryrolactone, isopropylidene ribonolactone, isocitric acid lactone, mannarolactone, sacharrodilactone and glucarodilactone.

11. A polymer bearing non-polymerizable lactone ring according to claim 4, wherein the polyorthoester is obtained from a diketene acetal and a dihydroxy non-polymerizable lactone ring bearing prepolymer.

12. A polymer bearing non-polymerizable lactone ring according to claim 11 wherein the dihydroxy non-polymerizable lactone ring bearing prepolymer comprises a polyester selected from the group consisting of polymers, copolymers or blends of l-lactide, dl-lactide, lactic acid,  $\epsilon$ -caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol.

13. A polymer bearing non-polymerizable lactone ring according to claim 5, wherein the polyphosphoester is obtained from ( $C_1$ - $C_{18}$ )alkylphosphodichloridates, cycloalkylphosphodichloridates or arylphosphodichloridates and a dihydroxy non-polymerizable lactone ring bearing prepolymer.

14. A polymer bearing non-polymerizable lactone ring according to claim 13 wherein the dihydroxy non-polymerizable lactone ring bearing prepolymer contains a polyester selected from the group consisting of polymers, copolymers or blends of l-lactide, dl-lactide, lactic acid,  $\epsilon$ -caprolactone, hydroxycaproic acid, p-dioxanone, trimethylene carbonate, 1,5-dioxepan-2-one, 1-4 dioxepan-2-one, glycolide, glycolic acid, ethylene glycol, propylene glycol valerolactone, hydroxyvaleric acid, and butanediol.

15. A polymer bearing non-polymerizable lactone ring according to claim 8, wherein the polyphosphazene is obtained from poly(dichloro)phosphazene and amino butyrolactone.

16. A polymer bearing non-polymerizable lactone ring according to claim 10, wherein the non-polymerizable lactone ring has been ring opened to its corresponding hydroxycarboxylic acid alkali metal salt.

17. A polymer bearing non-polymerizable lactone ring according to claim 16, wherein the hydroxycarboxylic acid alkali metal salt is within the polymer chain.

18. A complex comprising a polymer bearing non-polymerizable lactone ring according to claim 1, ionically complexed with a therapeutic agent containing at least one cationic group.

19. A complex comprising a polymer bearing non-polymerizable lactone ring according to claim 17, ionically complexed with a therapeutic agent containing at least one cationic group.

20. A complex according to claim 19, wherein the therapeutic agent is selected from the group consisting of LHRH, somatostatin, bombesin/GRP, calcitonin, bradykinins, galanin, MSH, GRF, amylin, tachykinin, secretin, PTH, CGRP, neuromedin, pTHRP, glucagon, neurotensin, ACTH, PYY, PYY, and TSH, or an analogue or fragment thereof.

21. A complex according to claim 20, wherein the therapeutic agent is a somatostatin analogue selected from the group consisting of H- $\beta$ -D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>, where the two Cys are bonded by a disulfide bond, N-hydroxyethylpiperazinyl-acetyl-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub> where the two Cys are bonded by a disulfide bond or N-hydroxyethylpiperazinyl-ethylsulfonyl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH<sub>2</sub> where the two Cys are bonded by a disulfide bond.

22. A complex according to claim 20, wherein the therapeutic agent is an LHRH analogue of the formula p-Glu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH<sub>2</sub>.

23. A sustained release composition comprising a complex according to claim 21 wherein the composition is in the form of microparticles, microspheres or rods.

24. A sustained release composition comprising a complex according to claim 22 wherein the composition is in the form of microparticles, microspheres or rods.



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25. A pharmaceutical composition comprising a sustained release composition according to claim 23 having an effective amount of the therapeutic agent and a pharmaceutically-acceptable carrier.

5 26. A pharmaceutical composition comprising a sustained release composition according to claim 24 having an effective amount of the therapeutic agent and a pharmaceutically-acceptable carrier.

10 27. A method of treating or preventing a disease or a condition, which comprises administering a pharmaceutical composition according to claim 25 to a patient in need thereof, wherein said disease or condition is a disease or condition that can be treated by the therapeutic agent in the pharmaceutical composition.

15 28. A method of treating or preventing a disease or a condition, which comprises administering a pharmaceutical composition according to claim 26 to a patient in need thereof, wherein said disease or condition is a disease or condition that can be treated by the therapeutic agent in the pharmaceutical composition.

20 29. A method of administering a pharmaceutical composition according to claim 25 to a recipient, wherein said pharmaceutical composition is administered orally, through the nasal passage, through the pulmonary passage or parenterally.

25 30. A method of administering a pharmaceutical composition according to claim 26 to a recipient, wherein said pharmaceutical composition is administered orally, through the nasal passage, through the pulmonary passage or parenterally.

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UKC  
WCT  
LXA

From the INTERNATIONAL SEARCHING AUTHORITY

To:  
FISH & RICHARDSON P.C.  
Attn. TSAO  
225 Franklin Street  
Boston, Massachusetts 02110  
UNITED STATES OF AMERICA

RECEIVED

APR 6 2000

FISH & RICHARDSON, P.C.  
BOSTON OFFICE

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 00537/184W01		Date of mailing (day/month/year) 31/03/2000
International application No. PCT/US 99/25706		FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant BIOMEASURE INCORPORATED et al.		International filing date (day/month/year) 02/11/1999

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 48):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

DOCKETED BY PATENT SYSTEMS  
Action Code Search Rpt (RSPN)  
Base Date 3/31/00  
Due Date 5/31/00  
Deadline

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Alfredo Prein

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## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

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## PATENT COOPERATION TREA

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>00537/184W01</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 99/ 25706</b>	International filing date (day/month/year) <b>02/11/1999</b>	(Earliest) Priority Date (day/month/year) <b>02/11/1998</b>
Applicant <b>BIOMEASURE INCORPORATED et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

## 4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

## 5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

## 6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/48 C08G64/00 C08G67/04 C08G79/02 C08G63/08

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C08G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 440 108 A (KANSAI PAINT CO LTD) 7 August 1991 (1991-08-07) preparation example 4 claims 1-9	1-3

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

23 March 2000

Date of mailing of the international search report

31/03/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Decocker, L

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/25706

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0440108 A	07-08-1991	JP 2098415 C	02-10-1996
		JP 3220238 A	27-09-1991
		JP 8016160 B	21-02-1996
		CA 2034865 A	26-07-1991
		DE 69118726 D	23-05-1996
		DE 69118726 T	29-08-1996
		EP 0673961 A	27-09-1995
		US 5629381 A	13-05-1997
		US 5696212 A	09-12-1997

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